



Exhibit B: CV of Paul S. Charifson, Ph.D.

Paul Scott Charifson, Ph.D.

Experience:

Vertex Pharmaceuticals, Inc., July 1997-present

- ❖ Director, Applications Modeling Group, Jan., 2001 - present
 - Insured that all project teams were well supported with modeling resources
 - Scientific direction and mentoring
 - Goal-setting and career development for group of 5-7 Ph.D. scientists
 - Budget setting and negotiation of software contracts
 - Interface with Modeling Methods Group for development of new software tools
- ❖ Project leader, Bacterial Topoisomerase (Gyrase B /Topoisomerase IV) drug discovery team, Dec., 1999-Dec., 2006
 - Responsible for scientific direction, goal setting, and budget for a team of 20+ scientists
 - Defined and drove compound optimization strategy
 - Provided computational chemistry support to team
 - Directed outsourcing of animal pharmacology and pharmacokinetics experiments
 - VX-692 was accepted into pre-clinical development Dec. 2004.
 - A second candidate was accepted into pre-clinical development Dec. 2005.
- ❖ Co-project leader, Caspase inhibitor project, Dec., 1998- Dec., 1999
 - Additionally provided computational chemistry support to team
 - VX-799 was accepted into pre-clinical development.
- ❖ Senior Staff Investigator, Project team member: key player in determining medicinal chemistry strategy for Interleukin-1 β Converting Enzyme (ICE) inhibitor project
 - Contributed to optimization of enzyme/cellular potency, and pharmacokinetic profile of pre-clinical candidate, VX-765, currently in Phase II.
 - Provided computational chemistry support to team
- ❖ Methods development for structure-based chemical library design, scoring functions, predicting cellular potency, flexible docking, 3D database generation, ADME prediction, ligand-based design

Glaxo Wellcome, Inc. September, 1991-June, 1996, Senior Scientist

- ❖ Modeling support for bone targeted estrogen program
- ❖ Inhibitors of src SH2 domain/ phosphoprotein interactions

- ❖ Key role in defining medicinal chemistry strategy and directing structural and biophysics experiments
- ❖ Nuclear Receptor Group
 - Successfully applied structure and non-structure based library design to identify selective ligands for all known subtypes of Peroxisome Proliferator Activated Receptors (PPARs)
 - Contributed to discovery of PPAR gamma clinical candidate
- ❖ Methods development for structure-based chemical library design, scoring functions, flexible docking, 3D database generation
- ❖ Computational Chemist, Cray Research, Inc., May, 1990-September 1991
 - Collaborative research with Glaxo, Burroughs-Wellcome, Environmental Protection Agency, and National Institute for Environmental Health Sciences on a variety of mechanistic and drug design projects

Education:

Post-Doctoral, Chemistry Department, University of North Carolina, Chapel Hill, NC, 1988-1990

Ph.D., Medicinal Chemistry, University of North Carolina, Chapel Hill, NC, 1988

Dissertation entitled, Synthesis, Molecular Modeling and Dopamine Receptor Affinity of Tetrahydroisoquinoline Derivatives

B.S., Pharmacy, University of Rhode Island, Kingston, RI, 1983

Computational Chemistry Skills:

Flexible and rigid-body docking, scoring function optimization, conformational searching and analysis, ligand-based design, de novo design, applied quantum mechanics, chemical library design and optimization, 2D and 3D database construction and retrieval, similarity and diversity evaluation, pharmacophore modeling, statistical inference, QSAR, molecular dynamics simulation, comparative protein homology model building, ADME prediction

Programming Skills: Perl, Awk, javascript, python

Editorial and Review Experience:

Book Editor: Practical Application of Computer-Aided Drug Design, Marcel-Dekker, July, 1997

Journal Reviewer: Journal of Computational Chemistry, Journal of Computer-Aided Molecular Design, Journal of Medicinal Chemistry, Proteins: Structure, Function, and Genetics

Patents and Patent Applications:

1. Wannamaker MW, Bemis GW, Charifson PS, Lauffer DJ, Mullican MD, Murcko MA., Wilson KP, Janetka JW, Davies RJ, Grillot A-L, Shi Z, Forster CJ. Preparation of peptides as inhibitors of caspases. PCT Int. Appl. (1999) WO 9947545 A2.
2. Wannamaker MW, Charifson PS, Lauffer DJ, Mullican MD. Preparation of 1,2-diazepanes as interleukin-1 β converting enzyme inhibitors. PCT Int. Appl. (1999) WO 9946248.
3. Charifson PS, Bellon S, Stamos D, Badia M, Grillot A-L, Ronkin S, Murcko M, Trudeau M. Preparation of 3-(phenylheterocyclyl)pyrazole DNA gyrase inhibitors as antibacterial agents. PCT Int. Appl. (2001) WO 2001052846 A1.
4. Charifson PS, Stamos, Dean, Badia, Michael, Grillot, Anne-laure, Ronkin, Steven, Trudeau, Martin. Preparation of 3-(phenylheterocyclyl)pyrazole DNA gyrase inhibitors as antibacterial agents. PCT Int. Appl. (2001), WO 2001052845 A1.
5. Golec J, Charifson PS, Charrier J-D, Binch H. Synthesis and use of heterocyclic substituted-amido halopentanoate derivatives as caspase inhibitors. PCT Int. Appl. (2001) WO 2001042216 A2.
6. Golec J, Charifson PS, Brenchley G. Preparation and use of 3-amido-4-oxo-5-halopentanoic acids and analogs as caspase inhibitors. PCT Int. Appl. (2001) WO 2001010383.
7. Grillot A-L, Charifson PS, Stamos D, Liao Y, Badia M, Trudeau M. Preparation of benzimidazoles as gyrase inhibitors. PCT Int. Appl. (2002) WO 2002060879 A2.
8. Charifson PS, Deininger DD, Drumm J, Grillot A-L, Liao Y, Oliver-Shaffer P, Stamos D. Preparation of 2-ureido-6-heteroaryl-3H-benzimidazole-4-carboxylic acid derivatives and related compounds as gyrase and/or topoisomerase IV inhibitors for the treatment of bacterial infections. PCT Int. Appl. (2003), WO 2003105846 A1.
9. Golec JMC, Charifson PS, Charrier J-D, Binch H. Synthesis of peptide heterocyclic derivatives as caspase inhibitors. U.S. Pat. Appl. Publ. (2003) US 2003232846 A1.
10. Charifson PS, Deininger DD, Grillot A-L, Liao Y, Ronkin SM, Stamos D, Perola E, Wang T, Letiran A, Drumm J. Preparation of benzimidazolyl ureas and related compounds as gyrase inhibitors for treating bacterial infections. U.S. Pat. Appl. Publ. (2004), US 2004235886 A1.
11. Charifson PS., Deininger DD., Grillot AL, Liao Y, Ronkin SM., Stamos D, Perola E, Wang, T, Letiran A, Drumm J. Preparation of annulated pyrazoles as gyrase inhibitors and uses thereof. U.S. Pat. Appl. Publ. (2005), 212 pp., Cont.-in-part of U.S. Ser. No. 971,573. US 2005256136 A1.
12. Charifson, PS, Deininger DD., Grillot A-L, Liao Y, Ronkin SM., Stamo, D, Perola E, Wang, T, Letiran, A, Drumm, J. Gyrase inhibitors and uses thereof. U.S. Pat. Appl. Publ. (2005) Cont.-in-part of U.S. Ser. No. 767,638. US 2005038247 A1.
13. Charifson, PS, Deininger DD, Grillot AL, Liao Y, Ronkin SM, Stamo, D, Perola E, Wang T, Letiran A, Drumm J. Preparation of benzimidazolyl ureas and related compounds as gyrase inhibitors for treating bacterial infections. U.S. Pat. Appl. Publ. (2004), US 2004235886 A1.

Book Chapters:

1. Molecular Dynamics Studies of H-ras p21-GTP, Foley, CK, Pedersen, LG, Darden, TA, Charifson, PS, Wittinghofer A, Anderson MW, in *GTPases in Biology*, Dickey BF, Birnbaumer L, Eds., *Handbook of Experimental Pharmacology* 108, Springer-Verlag, Berlin **1993**, Vol. 1., Chapter 16.
2. Recent Successes and Continuing Limitations in Computer-Aided Drug Design, Charifson PS, Kuntz ID, in *Practical Application of Computer-Aided Drug Design*, Charifson PS, Ed., Marcel Dekker, New York, **1997**, Chapter 1, pp1-37.
3. Structure-Based Drug Design, Murcko MA, Caron PR, Charifson PS, *Ann. Rep. Med. Chem.* Volume 34, **1999**, 297-306.
4. Filtering databases and chemical libraries, Charifson, PS, Walters, WP, in *Molecular Diversity* **2002** Vol. 5(4), 185-197.
5. An Analysis of Critical Factors Affecting Docking and Scoring, Perola, E, Walters WP, Charifson PS, in *Virtual Screening in Drug Discovery*, Alvarez, J and Shoichet, BK, Eds., **2005**, Chapter 3, pp 45-70.

Publications:

1. Synthesis and Pharmacological Characterization of 1-Phenyl-, 4-Phenyl-, and 1-Benzyl-1,2,3,4-Tetrahydroisoquinolines as Dopamine Receptor Ligands, Charifson PS, Wyrick SD, Hoffman AJ, Adame Simmons RM, Bowen JP, McDougald DL, Mailman RB, *J. Med. Chem.* **1988**, 31, 1941-1946.
2. Conformational Analysis and Molecular Modeling of 1-Phenyl-, 4-Phenyl-, and 1-Benzyl-1,2,3,4-Tetrahydroisoquinolines as Dopamine Receptor Ligands, Charifson PS, Bowen JP, Wyrick SD, Hoffman AJ, Cory M, McPhail AT, Mailman RB, *J. Med. Chem.* **1989**, 32, 2050-2058.
3. Pharmacological Effects of Tetrahydroisoquinoline Derivatives, Charifson PS, *Drugs of the Future* **1989**, 14, 1179-1185.
4. Synthesis and Characterization of 1,1,4,4-Butanetetra-carboxylic Acid: A di- γ -carboxyglutamic acid (Gla-Gla) Analogue, Cabaniss SE, Pugh K, Charifson PS, Pedersen LG, Hiskey RG, *Int. J. Peptide Prot. Res.* **1990**, 36, 79-85.
5. Construction and Molecular Modeling of Phospholipid Surfaces, Charifson PS, Hiskey RG, Pedersen LG, *J. Comp. Chem.*, **1990**, 11, 1181-1186.
6. Solution Conformations of the γ -Carboxyglutamic Acid Domain of Bovine Prothrombin Fragment 1, Residues 1-65, Charifson PS, Darden TA, Tulinsky A, Hughey JL, Hiskey RG, Pedersen LG, *Proc. Natl. Acad. Sci.* **1991**, 88, 424-428.
7. Free Energy Calculations on Calcium and Magnesium Complexes: Protein and Phospholipid Model Systems, Charifson PS, Hiskey RG, Pedersen LG, Kuyper LF, *J. Comp. Chem.* **1991**, 12(7), 899-908.
8. Expression and Characterization of Human Factor IX, Factor IX thr-397 and Factor IX val-397, Hamaguchi N, Charifson PS, Pedersen LG, Brayer GD, Smith K, Stafford D, *J. Biol. Chem.* **1991**, 266, 15213-15220.

9. Long Range Non-Bonded Attractive Constants for some Charged Atoms, Bartolotti LJ, Pedersen LG, Charifson PS, *J. Comp. Chem.* **1991**, 12(9), 1125-1128.
10. Simulation of the Solution Structure of the H-ras p21-GTP Complex, Foley CK, Pedersen LG, Charifson PS, Darden TA, Wittinghofer A, Pai EF, Anderson MW, *Biochemistry* **1992**, 31, 4951-4959.
11. Molecular Dynamics Simulations of Bovine Prothrombin Fragment 1 in the Presence of Calcium (II) Ions, Hamaguchi N, Charifson PS, Darden TA, Xiao L, Padmanabhan K, Tulinsky A, Hiskey RG, Pedersen LG, *Biochemistry* **1992**, 31, 8840-8848.
12. Cyclohexanediol Bisphosphonates as Models for Phospholipid-Metal Ion Binding Sites, Shuey S, Deerfield DW II, Amburgey JC, Cabaniss SE, Huh NW, Charifson PS, Pedersen LG, Hiskey RG, *Bioorganic Chem.* **1993**, 21(1), 95-108.
13. Computer-Assisted Molecular Modeling: Indispensable Tools for Molecular Pharmacology, Bowen JP, Charifson PS, Fox PC, Kontoyanni M, Miller AB, Schnur D, Stewart EL, Van Dyke C, *J. Clin. Pharm.* **1993**, 33, 1149-1164.
14. Role of Gln-61 in the Hydrolysis of GTP by p21^{H-ras}: An Experimental and Theoretical Study, Frech M, Darden TA, Pedersen LG, Coley CK, Charifson PS, Anderson MW, Wittinghofer A, *Biochemistry* **1994**, 33, 3237-3244.
15. Conformational Analyses, Pharmacophore Identification and Comparative Field Analyses of Ligands for the Neuromodulatory σ_3 Receptor, Myers A M, Charifson PS, Owens CE, Kula NS, McPhail AT, Baldessarini RJ, Booth RG, Wyrick SD, *J. Med. Chem.* **1994**, 37, 4109-4117.
16. Peptide Inhibitors of src SH3-SH2/Phosphoprotein Interactions, Gilmer T, Rodriguez M, Jordan S, Crosby R, Alligood K, Green M, Kimery M, Wagner C, Kinder D, Charifson P, Hassel A, Willard D, Luther M, Rusnak D, Sternbach D, Mehrotra M, Peel M, Shampine L, Davis R, Robbins J, Patel I, Kassel D, Burkhart W, Moyer M, Bradshaw T, Berman J, *J. Biol. Chem.* **1994**, 269(50), 31711-31719.
17. 3-[4-(1,2-Diphenyl-but-1-enyl)-phenyl]-acrylic acid: A Non-Steroidal Estrogen with Functional Selectivity for Bone over Uterus in Rats, Willson TM, Henke BR, Momtahn TM, Charifson PS, Batchelor KW, Lubahn DB, Moore LB, Oliver BB, Sauls HR, Triantafillou JA, Wolfe SG, Baer PG, *J. Med. Chem.* **1994**, 37, 1550-1552.
18. Synthesis and Molecular Modeling of 1-Phenyl-1,2,3,4-Tetrahydroisoquinolines and Related 5,6,8,9--Tetrahydro-13-bH-Dibenzo[a,h]quinazolines as D₁ Dopamine Antagonists, Minor DL, Wyrick SD, Charifson PS, Watts VJ, Nichols DE, Mailman RB, *J. Med. Chem.* **1994**, 37, 4317-4328.
19. The Generation and Use of Large 3D Databases in Drug Discovery, Charifson PS, Leach AR, Rusinko AR III, *Network Science* **1995**, 1(3),
URL=<http://www.netsci.org/Science/Cheminform/feature03.html>.
20. Bone Targeted Drugs. 1. Identification of Heterocycles with Hydroxyapatite Affinity, Willson TM, Charifson PS, Baxter AD, Geddie NG, *Bioorg. Med. Chem. Lett.* **1996**, 6(9), 1043-1046.
21. α -Dicarbonyls as Non-Charged Arginine-Directed Affinity Labels. Novel Synthetic Routes to α -Dicarbonyl Analogs of the pp60^{c-src} SH2 Domain-Targeted

Phosphopeptide Ac-Tyr(OPO₃H₂)-Glu-Glu-Ile-Glu, Mehrotra MM, Sternbach DD, Rodriguez M, Charifson PS, Berman J, *Bioorg.Med.Chem.Lett.* **1996**, 6(16), 1941-1946.

22. Peptide Ligands of pp60^{c-src} SH2 Domains: A Thermodynamic and Structural Study, Charifson PS, Shewchuk LM., Rocque W, Hummel CW, Jordan SR, Mohr C, Pacofsky GJ, Peel MR, Rodriguez M, Sternbach DD, Consler TG, *Biochemistry* **1997**, 36, 6283-6293.

23. Identification of Peroxisome Proliferator-Activated Receptor Ligands from a Biased Chemical Library, Brown PJ, Smith-Oliver TA, Charifson PS, Tomkinson NC, Fivush AM, Sternbach DD, Wade LE, Orband-Miller L, Parks DJ, Blanchard SG, Klier SA, Lehmann JM, Willson TM, *Chem. Biol.* **1997**, 4(12), 909-918.

24. The Formation of a Covalent Complex Between a Dipeptide Ligand and the src SH2 Domain, Alligood K, Charifson PS, Crosby R, Consler TG, Feldman PL, Gampe RT, Gilmer T, Jordan S, Milstead MW, Mohr C, Peel MR, Rocque W, Rodriguez M, Rusnak DW, Shewchuk LM, Sternbach DD, *Bioorg.Med.Chem Lett.* **1998**, 8, 1189-1194.

25. Potent Dipeptide Inhibitors of the pp60^{c-src} SH2 Domain, Pacofsky GJ, Lackey K, Alligood KJ, Berman J, Charifson PS, Crosby RM, Dorsey GF, Feldman PL, Gilmer TM, Hummel CW, Jordan SR, Mohr C, Shewchuk LM, Sternbach DD, Rodriguez M, *J. Med. Chem.* **1998**, 41(11), 1894-1908.

26. N-(2-Benzoylphenyl)-L-tyrosine PPAR gamma agonists. 3. Structure-activity relationship and optimization of the N-aryl substituent, Cobb JE, Blanchard SG, Boswell EG, Brown KK, Charifson PS, Cooper JP, Collins JL, Dezube M, Henke BR, Hull-Ryde EA, Lake DH, Lenhard JM, Oliver W Jr, Oplinger J, Pentti M, Parks DJ, Plunkett KD, Tong WQ. *J Med Chem.* **1998** 41(25): 5055-69.

27. N-(2-Benzoylphenyl)-L-tyrosine PPAR gamma agonists. 2. Structure-activity relationship and optimization of the phenyl alkyl ether moiety, Collins JL, Blanchard SG, Boswell GE, Charifson PS, Cobb JE, Henke BR, Hull-Ryde EA, Kazmierski WM, Lake DH, Leesnitzer LM, Lehmann J, Lenhard JM, Orband-Miller LA, Gray-Nunez Y, Parks DJ, Plunkett KD, Tong WQ. *J Med Chem.* **1998** 41(25): 5037-54.

28. Consensus scoring: A method for obtaining improved hit rates from docking databases of three-dimensional structures into proteins, Charifson PS, Corkery JJ, Murcko MA, Walters WP, *J Med Chem.* **1999** 42(25): 5100-9.

29. The structures of caspases-1, -3, -7 and -8 reveal the basis for substrate and inhibitor selectivity, Wei Y, Fox T, Chambers SP, Sintchak J, Coll JT, Golec JM, Swenson L, Wilson KP, Charifson PS, *Chem Biol.* **2000** (6): 423-32.

30. Improved scoring of ligand-protein interactions using OWFEG free energy grids, Pearlman DA, Charifson PS, *J Med Chem.* **2001** 44(4): 502-11.

31. Are Free Energy Calculations Useful in Practice? A Comparison with Rapid Scoring Functions for the p38 MAP Kinase Protein System, Pearlman DA, Charifson PS, *J. Med. Chem.* **2001** 44(22): 3417-3423.

32. Filtering databases and chemical libraries, Charifson PS, Walters WP, *J. Comp-Aided Mol. Des.* **2002** 16(5/6), 311-323.

33. Active-site residues of Escherichia coli DNA gyrase required in coupling ATP hydrolysis to DNA supercoiling and amino acid substitutions leading to novobiocin resistance, Gross CH, Parsons JD, Grossman TH, Charifson PS, Bellon S, Jernee J, Dwyer M, Chambers SP, Markland W, Botfield M, Raybuck S, *Antimicrob. Agents Chemother.* **2003** 47(3), 1037-1046.
34. A detailed comparison of current docking and scoring methods on systems of pharmaceutical relevance, Perola E, Walters WP, Charifson PS, *Proteins: Structure, Function, and Bioinformatics* **2004** 56(2), 235-249.
35. Conformational Analysis of Drug-Like Molecules Bound to Proteins: An Extensive Study of Ligand Reorganization upon Binding, Perola E, Charifson PS, *J. Med. Chem.* **2004** 47(10), 2499-2510.
36. Crystal structures of Escherichia coli topoisomerase IV ParE subunit (24 and 43 kilodaltons): a single residue dictates differences in novobiocin potency against topoisomerase IV and DNA gyrase, Bellon S, Parsons JD, Wei Y, Hayakawa K, Swenson LL, Charifson PS, Lippke JA, Aldape R, Gross CH, *Antimicrob. Agents Chemother.* **2004** 48(5), 1856-1864.
37. VX-765, an orally available selective interleukin converting enzyme (ICE)/caspase-1 inhibitor exhibits potent anti-inflammatory activities by inhibiting the release of IL-1 β and IL-18, Wannamaker W, Davies R, Namchuk M, Charifson PS, Pollard J, Ford P, Ku G, Decker C, Germann UA, Kuida K and Randle CR (submitted, *J Pharm. Exp. Ther.*)
38. Characterization of the Antibacterial Spectrum of a Novel Class of Bacterial Type II Topoisomerase Inhibitors, Nagraj M, Gross CH, Parsons JD, Hanzelka B, Müh U, Mullin S, Liao Y, Grillot A-L, Stamos D, Charifson PS and Grossman TH (in press, *Antimicrob. Agents Chemother.*).
39. Dual-targeting of GyrB and ParE by VRT-125856 and VRT-752586, Representatives of a Novel Class of Antibacterial Compounds, Grossman TH, Bartels D, Mullin S, Gross CH, Parsons JD, Liao Y, Grillot A-L, Stamos D, Olson E, Charifson PS, and Mani N (manuscript in preparation).